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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/636,259	Applicant(s) SMALL ET AL.	
	Examiner Diana B. Johannsen	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *4-61 and 66-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *30 October 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,19* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *22* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Search Results* .

DETAILED ACTION

1. The paper and computer readable forms of the Sequence Listing filed March 6, 2003 have been entered.

Election/Restriction

2. Applicant's election with traverse of Group I, claims 1-3 and 62-65 in Paper No. 20 is acknowledged. The traversal is on the ground(s) that "it would not be unduly burdensome for the Examiner to examine claims 4-61 and 66-69 with claims 1-3 and 62-65." This argument has been thoroughly considered but is not found persuasive. *MPEP* 803 states that "a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search." In the Election/Restriction of paper no. 18, the examiner provided a detailed explanation of how and why Inventions I-VIII (as well as the various primer pairs of Invention III) were distinct from one another, and stated that:

> Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, and because Inventions I-VIII, as well as the various primer pairs of Invention III, require different sequence and text searches that are not co-extensive, examination of these distinct Inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

Accordingly, the examiner established in the Election/Restriction that examination of the distinct inventions claimed by applicant would constitute an undue burden. *MPEP* 803 further states that the examiner's *prima facie* showing of a serious burden "may be rebutted by appropriate showings or evidence by the applicant." However, applicant's

statement that "it would not be unduly burdensome for the Examiner to examine claims 4-61 and 66-69 with claims 1-3 and 62-65" does not constitute such a showing, and applicant has not provided any evidence to support the assertion that examination of all the pending claims would not be unduly burdensome. Further, applicant has not distinctly and specifically pointed out any supposed errors in the restriction requirement. Accordingly, applicant's arguments are not persuasive.

Clmgs 4-7-03

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4-61 and 66-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 20.

Information Disclosure Statement

4. Regarding the information disclosure statement filed April 9, 2001, paper no. 4, it is noted that the examiner has provided complete citations for the last reference on sheet 2 (by adding the names of inventors that were omitted from the citation) and for the last two references on sheet 4 (by adding additional identifying information regarding the information obtained from the cited web addresses)(see the signed, initialed copy of the 1449 enclosed herewith). Regarding the two cited web addresses, it is also noted that applicant has provided printouts of the information obtained on the "visited" date recited on the 1449, and that these printouts (not the websites themselves) were considered by the examiner.

Drawings

5. The drawings are objected to because the sequences depicted in panels A-C of Figure 1 are not fully legible in the Figure 1 depicting proposed corrections filed October 30, 2002. It is noted that applicant's proposed corrections of Figures 1-2 have been approved, and that corrected drawings are required in response to this Office action. However, in the substitute drawings, applicant should ensure that the sequences depicted in Figure 1 are clear and fully legible.

It is also noted that Figures 3-6, as filed August 10, 2000, are accepted by the Examiner.

Corrected drawings (specifically, Figures 1-2) are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

6. The disclosure is objected to because of the following informalities. The Brief Description of Figure 1 incorrectly states that Panel C shows an agarose gel; further, the Description refers to panels A-C, but does not include a description of Panel D. It appears that the description includes a typographical error, such that it refers twice (once erroneously) to panel C, and fails to refer to panel D. This objection could be overcome by amending page 8, line 13 such that it recites "Panel D shows an agarose gel...." Correction is required.

It is also noted that applicant's proposed drawing corrections to Figures 1 and 2 have been approved, and that corrected drawings are required in response to this Office

action. Accordingly, the Brief Description of Figure 2 must be amended such that it corresponds to the substitute Figure 2 that will be provided in response to this Office action.

Appropriate correction is required.

7. The use of the trademark QIAQUICK™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polynucleotides comprising SEQ ID NO: 1 or SEQ ID NO: 2, as well as isolated polynucleotides including fragments and/or complements of SEQ ID NO: 1 or 2 which polynucleotides specifically hybridize to and detect either SEQ ID NO: 1 or SEQ ID NO: 2, does not reasonably provide enablement for isolated polynucleotides comprising "SEQ ID NO: 1 or 2 or fragment or complement thereof," which polynucleotides comprise "at least one polymorphic site." The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

The claims are drawn to an "isolated polynucleotide encoding an alpha-2A adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement thereof, wherein the polynucleotide comprises at least one polymorphic site." Claim 2 further requires that "the polymorphic site comprises cytosine or guanine at nucleotide position 753 of SEQ ID NO: 1 or 2," while claim 3 further requires that "the polymorphic site occurs in human chromosome 10."

The specification discloses that the alpha-2A adrenergic receptor (alpha-2A-AR) is a plasma membrane receptor that is involved in signal transduction and is known to be targeted by agonists such as epinephrine and norepinephrine, as well as synthetic agonists and antagonists, and particularly antihypertensive agents (see, e.g., p. 1-3, p. 10-12). The specification discloses the coding sequence of the wild-type alpha-2A-AR

gene (SEQ ID NO: 1; see, e.g., page 15), as well as the coding sequence of a variant alpha-2A-AR gene (SEQ ID NO: 2) that includes a C753G polymorphism which encodes an Asn251Lys substitution in the alpha-2A-AR protein of individuals having the variant gene (see, e.g., Table A on page 16). The specification provides evidence that the presence of Lys251 is associated with significant differences in responses to various hormones and drugs (see, e.g., pages 46-47, Figures 3-5, Examples 3-5). Accordingly, given the guidance provided in the specification, the genotype of the alpha-2A-AR gene at position 753 would be one factor that one of skill in the relevant art would reasonably consider in selecting appropriate drug therapies and dosages, as asserted by applicant, and it would be well within the ability of one of skill in the art to employ both the wild type and the variant protein, nucleic acids encoding these proteins (e.g., SEQ ID NOs: 1 and 2), and polynucleotides that specifically hybridize to and detect SEQ ID NO: 1 and SEQ ID NO: 2, in, e.g., methods of selecting patient treatments and therapies. However, it is unpredictable as to whether one of skill in the art could make and use the invention in a manner reasonably commensurate with the instant claims.

The instant claims are not limited to polynucleotides that encode the wild-type and variant proteins disclosed in the specification, or to, e.g., molecules that specifically hybridize to and detect such polynucleotides. Rather, the claims encompass isolated polynucleotides "encoding an alpha-2A adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or fragment or complement thereof," which polynucleotide comprises "at least one polymorphic site." It is first noted that the claims as written do not require the presence of a nucleotide that differs from the wild-type, but rather encompass any

molecule that includes any "polymorphic site." Further, the claims are not limited to molecules encoding the particular variant protein disclosed in the specification, but rather embrace molecules encoding any variant of alpha-2A-AR. The claims do not require molecules that encode an alpha-2A-AR; rather the claims require a polynucleotide "encoding an alpha-2A adrenergic receptor molecule." While the specification does indicate that such molecules include molecules that "specifically hybridize to nucleic acid molecules encoding the alpha-2A-adrenergic receptor," the specification also teaches that such molecules include "fragments, portions, and segments" of full length molecules that do not have this functional property (see page 18). Additionally, the claims embrace molecules comprising any "fragment or complement" of SEQ ID NO: 1 or SEQ ID NO: 2 including any type of "polymorphic site." While the specification does indicate that "fragments" of the invention must be "readily identifiable by the molecular techniques" described in the specification (see page 17), the specification does not define the term "fragment" in such a way that it is limited to molecules having particular functional properties, and any type of fragment would be "identifiable" using the general methods disclosed in the specification. Thus, the claims as written are sufficiently broad so as to encompass, e.g., polynucleotides comprising small portions of the alpha-2A-AR gene (e.g., 10mers, 12mers) including any type of "polymorphic site," which site might or might not have any association with drugs responses in patients. With further regard to claim 2, while the claim does require that "the polymorphic site comprises cytosine or guanine at nucleotide position 753 of SEQ ID NO: 1 or 2," the claim as written is not limited to, e.g., fragments of SEQ ID NO:

1 or 2 that include position 753 and a particular amount of flanking sequence, or to molecules that specifically hybridize to and detect SEQ ID NO: 2/the particular variant gene disclosed in the specification, such that the claim is clearly limited to molecules useful in the methods disclosed by applicant. Thus, while the specification exemplifies a few particular molecules useful in methods of selecting drug dosages and therapies, the instant claims are very broad, encompassing numerous molecules that would not be useful in distinguishing or differentiating the particular alpha-2A-AR variant disclosed in the specification from wild-type alpha-2A-AR, and therefore not useful in the methods described by applicant. Accordingly, while the teachings of the specification would enable one of skill in the art to use isolated polynucleotides comprising SEQ ID NO: 1 or SEQ ID NO: 2, as well as isolated polynucleotides including fragments and/or complements of SEQ ID NO: 1 or 2 which polynucleotides specifically hybridize to and detect either SEQ ID NO: 1 or SEQ ID NO: 2, the guidance provided by the specification is insufficient to allow one of skill in the art to use the invention as now claimed.

Absent guidance from the specification, one of skill in the art may look to the teachings of the prior art for further guidance and enablement of a claimed invention. Like applicant, the prior art discloses the wild-type alpha 2A-AR gene, the coding sequence of which is described by applicant as SEQ ID NO: 1 (see the discussion of Fraser et al (The Journal of Biological Chemistry 264(20):11754-11761 [7/1989]) and Guyer et al (The Journal of Biological Chemistry 265(28):17307-17317 [10/1990]) in paragraph 13, below). It is also noted that the prior art as exemplified by Fraser et al discloses genomic sequence flanking the alpha-2A-AR gene and establishes that the

gene is intronless (see, e.g., pages 11755-11756 and Figure 2 of Fraser et al). Further, the prior art does disclose other polymorphisms in the alpha-2A-AR gene. For example, Feng et al (American Journal of Medical Genetics (Neuropsychiatric Genetics) 81:405-410 [1998]) teach six particular polymorphisms in the alpha-2A-AR gene that were identified in psychiatric patients (see entire reference). The polymorphisms disclosed by Feng et al include polymorphisms that cause four different missense mutations, as well as a silent coding region polymorphism and a 3' untranslated region polymorphism, and include the polymorphism described by applicants as the C753G polymorphism, which polymorphism results in the Asn251Lys substitution (see, e.g., Table II of Feng et al; see also paragraph 14, below). However, Feng et al do not provide evidence that any of these polymorphisms is associated with altered responses to hormones or drugs. While Feng et al propose that the substitutions of amino acids 268 and 270 are "likely to be of functional significance," Feng et al clearly teach that further study is required to determine whether these polymorphisms are actually associated with adrenergic dysfunction, predisposition to substance abuse, and/or other clinical traits such as response to pharmacotherapy (see pages 408-410, particularly page 409, right column). Further, Feng et al do not indicate that any of the other 4 polymorphisms identified are likely to be of clinical significance (see entire reference). Accordingly, Feng et al do not provide evidence of the existence any other alpha-2A-AR molecules comprising "polymorphic sites" that one of skill in the art would consider to be useful in the methods disclosed and exemplified by applicant. Given the high level of skill of one of skill in the relevant art, it is clearly within the ability of such an artisan to conduct further

experimentation in order to further characterize other polymorphisms known in the art (e.g., those of Feng et al), as well as to detect additional polymorphisms and . "polymorphic sites" within the human alpha-2A-AR gene, and to determine whether mutations are or are not associated with differences in drug responses. However, the outcome of such further experimentation cannot be predicted, and further, it is well known to those of skill in the art that many gene polymorphisms have no effect on protein structure, function, or expression. Thus, until other alpha-2A-AR polymorphisms are identified and analyzed for possible associations with drug and hormone response, it is unpredictable as to whether other polymorphisms of the type described by applicant even exist. Accordingly, it is unpredictable as to whether any quantity of experimentation would be sufficient to allow one of skill in the art to use applicant's invention as now claimed. While one of skill in the art could make and use isolated polynucleotides comprising SEQ ID NO: 1 or SEQ ID NO: 2, as well as isolated polynucleotides including fragments and/or complements of SEQ ID NO: 1 or 2 which polynucleotides specifically hybridize to and detect either SEQ ID NO: 1 or SEQ ID NO: 2 in the methods described by applicant, it would require undue experimentation to make and use the claimed invention.

Regarding claim 2, it is again noted that the claim is not limited to, e.g., fragments of SEQ ID NO: 1 or 2 that include position 753 and a particular amount of flanking sequence, or to molecules that specifically hybridize to and detect SEQ ID NO: 2/the particular variant gene disclosed in the specification, such that the claim is clearly limited to molecules useful in the methods disclosed by applicant. With further respect

to claim 3, it is noted that it is an inherent property of the human alpha-2A-AR gene (and any "polymorphic site" contained therein) that it is located on human chromosome 10. Accordingly, the recitation of claim 3 does not further limit the structural or functional properties of the "isolated polynucleotide" of the claims.

It is noted that this rejection could be overcome by clearly limiting the instant claims to isolated polynucleotides that could be employed in differentiating SEQ ID Nos 1 and 2 (e.g., to SEQ ID NO: 2, to fragments of SEQ ID NO: 2 that include nucleotide 753 and sufficient flanking sequence such that the fragments specifically hybridize to and detect the variant polynucleotide, etc.).

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 2-3 and 62-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite over the recitation of the phrase "wherein the polymorphic site comprises cytosine or guanine at nucleotide position 753 of SEQ ID NO: 1 or 2." First, it is noted that claim 1, from which claim 2 depends, is not limited to molecules that comprise or consist of SEQ ID NO: 1 or 2. Accordingly, it is unclear as to how this recitation would further limit a polynucleotide that comprises a fragment or complement of SEQ ID NO: 1 or 2 (i.e., how would one identify "position 753 of SEQ ID NO: 1 or 2" if SEQ ID NO: 1 or SEQ ID NO: 2 is not actually present?). Further, the recitation "the polymorphic site comprises cytosine or guanine" is confusing. It is unclear as to

whether this recitation is intended to indicate that either a cytosine or a guanine is located at position 753, or whether the language "polymorphic site comprises" is intended to allow the inclusion of additional nucleotides, variations, etc., within a particular "site" in a molecule. Additionally, as claim 1 recites "at least one polymorphic site" (rather than a single "polymorphic site"), it is unclear as to whether the recitation "the polymorphic site" in claim 2 is intended to further limit the "at least one polymorphic site" of claim 1, or whether this recitation is intended to further limit, e.g., a single polymorphic site which may be encompassed by the recitation of "at least one polymorphic site" in claim 1. Clarification is required.

Claim 3 is indefinite over the recitation of the phrase "wherein the polymorphic site occurs in human chromosome 10" because it is unclear as to how this recitation is intended to further limit the claimed invention. The claim is drawn to an "isolated polynucleotide" that "comprises at least one polymorphic site." Accordingly, it is unclear as to how a requirement that the polymorphic site "occurs" in a particular human chromosome might further limit the structural or functional characteristics of the claimed isolated molecule. Additionally, as claim 1 recites "at least one polymorphic site" (rather than a single "polymorphic site"), it is unclear as to whether the recitation "the polymorphic site" in claim 3 is intended to further limit the "at least one polymorphic site" of claim 1, or whether this recitation is intended to further limit, e.g., a single polymorphic site which may be encompassed by the recitation of "at least one polymorphic site" in claim 1. Clarification is required.

Claims 62-63 are indefinite over the recitation of the limitation "the alpha-2A adrenergic receptor molecule comprising SEQ ID NO: 2" in claim 62 because there is insufficient antecedent basis for this limitation in the claims. This rejection could be overcome by amending the claim to recite "an alpha-2A adrenergic receptor...."

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Fraser et al (The Journal of Biological Chemistry 264(20):11754-11761 [7/1989]), in light of the teachings of Guyer et al (The Journal of Biological Chemistry 265(28):17307-17317 [10/1990]) .

It is first noted that instant SEQ ID Nos 1 and 2 are identical to one another with the exception of the nucleotide located at position 753. SEQ ID NO: 1 includes a C at this position and encodes the wild-type alpha-2A adrenergic receptor having an asparagine at amino acid 251, while SEQ ID NO: 2 includes a G at this position and encodes a variant of the alpha-2A adrenergic receptor having a lysine at amino acid 251 (see, e.g., page 8 of the specification).

Fraser et al teach an isolated polynucleotide that comprises a nucleotide sequence that is identical to instant SEQ ID NO: 1, and that is identical to instant SEQ

ID NO: 2 with the exception of having a C rather than a G at the position corresponding to position 753 of instant SEQ ID NO: 2 (see Figure 2 and page 11755). It is noted that an alignment of the sequence disclosed by Fraser et al with instant SEQ ID NOs: 1 and 2 indicates the presence of an insertion at nucleotide 997 and a deletion after nucleotide 1093 in SEQ ID NOS 1 and 2 as compared to the sequence of Fraser et al (see the alignments enclosed herewith; see also paragraph 18, below). However, Guyer et al disclose that the sequence published by Fraser et al contains errors at these positions, such that the molecule disclosed by Fraser et al is actually identical to instant SEQ ID NOS 1-2 at these locations (see page 17311 of Guyer et al; see also reference no. 6 cited by Guyer et al, which is the instant Fraser et al reference). Accordingly, the teachings of Guyer et al establish that it is an inherent property of the isolated polynucleotide taught by Fraser et al that it comprises a nucleotide sequence that is identical to instant SEQ ID NO: 1, and that is identical to instant SEQ ID NO: 2 with the exception of having a C rather than a G at the position corresponding to position 753 of instant SEQ ID NO: 2, as set forth above.

While Fraser et al do not refer to their gene as an alpha-2A adrenergic receptor molecule, the gene is identical to the molecule disclosed by applicant as SEQ ID NO: 1 (as discussed above), and it is an inherent property of the molecule of Fraser et al that it is an "alpha-2A adrenergic receptor molecule," as required by the claims. Further, as position 753 of SEQ ID NO: 1 and SEQ ID NO: 2 is disclosed by applicant to be a "polymorphic site" that meets the requirements of the claims (see, e.g., claim 2), the molecule of Fraser et al – which includes this "polymorphic site" – comprises "at least

one polymorphic site," as recited in claim 1. With further respect to claim 2, the molecule of Fraser et al includes a G at the position described by applicant as position 753 of SEQ ID NO: 1/SEQ ID NO: 2, and therefore the molecule of Fraser et al is a molecule in which "the polymorphic site comprises cytosine or guanine at nucleotide position 753 of SEQ ID NO: 1 or 2," as required by the claim. Regarding claim 3, as it is an inherent property of the gene disclosed by Fraser et al that it is located on human chromosome 10, it is an inherent property of the "polymorphic site" of Fraser et al that it meets the limitations of the claim. Accordingly, Fraser et al clearly anticipate claims 1-3.

14. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Feng et al (American Journal of Medical Genetics (Neuropsychiatric Genetics) 81:405-410 [1998]), in light of Fraser et al and Guyer et al.

Feng et al disclose multiple different isolated polynucleotides that are encompassed by the instant claims, as described in detail below (see entire reference).

Feng et al disclose isolated polynucleotides prepared by PCR amplification that comprise the complete coding sequence of the human alpha-2A-AR gene (see pages 407-408, particularly page 407, right column and page 408, left column). Feng et al employ their polynucleotides - which include amplification products prepared from 206 different psychiatric patients – in a method of screening for novel mutations in the alpha-2A-AR gene, which method "can detect virtually 100% of mutations in DNA segments as large as 2kb" (see page 407, left column). Feng et al disclose that their method identified 6 different polymorphisms, 5 of which were found in only one patient (see page 408, particularly Table II). Accordingly, the isolated polynucleotides disclosed by

Feng et al include polynucleotides comprising wild-type alpha-2A-AR coding sequences (i.e., amplification products from patients exhibiting no mutations/polymorphisms) and well as several different variant polynucleotides, which variant polynucleotides include the polymorphisms recited in Table II of the reference.

First, it is noted that the specification indicates that instant SEQ ID NO: 1 depicts the wild-type human alpha-2A-AR gene coding sequence (see, e.g., page 15 of the specification). Further, as discussed in paragraph 13, above, the prior art establishes that it is an inherent property of the human wild-type alpha-2A-AR coding sequence that it has the sequence described by applicant as SEQ ID NO: 1. (Specifically, as discussed in paragraph 13, Fraser et al discloses that the wild-type alpha-2A-AR coding sequence is identical to instant SEQ ID NO: 1 with the exception of a single deletion and a single insertion, and Guyer et al disclose that these two sequence difference are errors, such that the wild-type sequence of alpha-2A-AR is actually 100% identical to instant SEQ ID NO: 1.) Accordingly, it is an inherent property of the isolated polynucleotides of Feng et al that are free of polymorphisms that these molecules constitute isolated polynucleotides comprising instant SEQ ID NO: 1. As these molecules of Feng et al include the "polymorphic site" identified by applicant as position 753, as well as other polymorphic sites that correspond to the locations of novel polymorphisms identified by Feng et al, the wild-type molecules taught by Feng et al meet the requirements of claims 1-3.

Second, Feng et al disclose an isolated polynucleotide encoding alpha-2A-AR that includes a C752G polymorphism that encodes an Asn251Lys substitution (see,

e.g., Table 2). It is noted that Feng et al refer to nucleotide 752, while the polymorphism disclosed by applicant that encodes Asn251Lys is described as occurring at nucleotide 753. However, an inspection of Figure 2 of Fraser et al (which employs the numbering system used by Feng et al; see the footnotes of Table II of Feng et al) reveals that nucleotide 752 of Feng et al is in fact the same nucleotide described by applicant as nucleotide 753; the polymorphism in both cases results in the alteration of an AAC codon (encoding an asparagines at amino acid 251) to an AAG codon (encoding lysine at amino acid 251)(see Fraser et al, Figure 2). Further, it is noted that Feng et al teach that the method they employed "can detect virtually 100% of mutations in DNA segments as large as 2kb" (see page 407), and that Feng et al do not disclose the presence of any other polymorphisms in the alpha-2A-AR polynucleotide of the particular schizophrenia patient possessing the C752G polymorphism. Accordingly, as this single nucleotide change is also the only difference in instant SEQ ID NO: 2 as compared to instant SEQ ID NO: 1, Feng et al also inherently disclose an isolated polynucleotide comprising instant SEQ ID NO: 2. This molecule disclosed by Feng et al also meets the requirements of claims 1-3.

Finally, it is again noted that Feng et al disclose multiple variant alpha-2A-AR molecules. In several cases, the polymorphisms disclosed by Feng et al are described as being found in a single individual (see Table II), and Feng et al does not indicate that any of these individuals was found to possess multiple polymorphisms. Each such variant polynucleotide constitutes an isolated polynucleotide that comprises "SEQ ID NO: 1" and further comprises "at least one polymorphic site." Further, while all but one

of these molecules lacks the nucleotide 752 polymorphism disclosed by Feng et al, each of these molecules includes position 752, which is a "polymorphic site." Accordingly, each of these molecules meets the requirements of claim 2, as the claim as written encompasses any molecule including the recited "polymorphic site" (i.e., molecules encompassed by the claim may include either the wild-type cytosine or the variant guanine). Regarding claim 3, it is again noted that as it is an inherent property of the alpha-2A-AR gene that it is located on human chromosome 10, it is an inherent property of any "polymorphic site" of the gene that it meets the limitations of the claim.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feng et al (American Journal of Medical Genetics (Neuropsychiatric Genetics) 81:405-410 [1998]) in view of Fraser et al (The Journal of Biological Chemistry 264(20):11754-11761 [7/1989]), in light of the teachings of Guyer et al (The Journal of Biological Chemistry 265(28):17307-17317 [10/1990]).

It is again noted that instant SEQ ID Nos 1 and 2 are identical to one another with the exception of the nucleotide located at position 753. SEQ ID NO: 1 includes a C at this position and encodes the wild-type alpha-2A adrenergic receptor having an asparagine at amino acid 251, while SEQ ID NO: 2 includes a G at this position and encodes a variant of the alpha-2A adrenergic receptor having a lysine at amino acid 251 (see, e.g., page 8 of the specification).

Feng et al disclose isolated polynucleotides prepared by PCR amplification that comprise the complete coding sequence of the human alpha-2A-AR gene (see pages 407-408, particularly page 407, right column and page 408, left column). Feng et al employ their polynucleotides - which include amplification products prepared from 206 different psychiatric patients – in a method of screening for novel mutations in the alpha-2A-AR gene, which method "can detect virtually 100% of mutations in DNA segments as large as 2kb" (see page 407, left column). Feng et al disclose that their method identified 6 different polymorphisms, 5 of which were found in only one patient (see page 408, particularly Table II). Accordingly, the isolated polynucleotides disclosed by Feng et al include polynucleotides comprising wild-type alpha-2A-AR coding sequences (i.e., amplification products from patients exhibiting no mutations/polymorphisms) and

well as several different variant polynucleotides, which variant polynucleotides include the polymorphisms recited in Table II of the reference.

It is first noted that the specification indicates that instant SEQ ID NO: 1 depicts the wild-type human alpha-2A-AR gene coding sequence (see, e.g., page 15 of the specification). Further, as discussed in paragraph 13, above, the prior art establishes that it is a property of the human wild-type alpha-2A-AR coding sequence that it has the sequence described by applicant as SEQ ID NO: 1. (Specifically, as discussed in paragraph 13, Fraser et al disclose that the wild-type alpha-2A-AR coding sequence is identical to instant SEQ ID NO: 1 with the exception of a single deletion and a single insertion, and Guyer et al disclose that these two sequence differences are errors, such that the wild-type sequence of alpha-2A-AR is actually 100% identical to instant SEQ ID NO: 1.) Accordingly, it is a property of the isolated polynucleotides of Feng et al that are free of polymorphisms that these molecules constitute isolated polynucleotides comprising instant SEQ ID NO: 1.

Feng et al disclose an isolated polynucleotide encoding alpha-2A-AR that includes a C752G polymorphism that encodes an Asn251Lys substitution (see, e.g., Table 2). It is noted that Feng et al refer to nucleotide 752, while the polymorphism disclosed by applicant that encodes Asn251Lys is described as occurring at nucleotide 753 in SEQ ID NO: 1/SEQ ID NO: 2. However, an inspection of Figure 2 of Fraser et al (which employs the numbering system used by Feng et al; see the footnotes of Table II of Feng et al) reveals that nucleotide 752 of Feng et al is in fact the same nucleotide described by applicant as nucleotide 753; the polymorphism in both cases results in the

alteration of an AAC codon (encoding an asparagine at amino acid 251) to an AAG codon (encoding lysine at amino acid 251)(see Fraser et al, Figure 2). Further, it is noted that Feng et al teach that the method they employed "can detect virtually 100% of mutations in DNA segments as large as 2kb" (see page 407), and that Feng et al do not disclose the presence of any other polymorphisms in the alpha-2A-AR polynucleotide of the particular schizophrenia patient possessing the C752G polymorphism. Accordingly, as this single nucleotide change is also the only difference in instant SEQ ID NO: 2 as compared to instant SEQ ID NO: 1, Feng et al disclose an isolated polynucleotide comprising instant SEQ ID NO: 2. Specifically, it is a property of the isolated amplification product of schizophrenia patient S589 disclosed by Feng et al that it comprises the sequence disclosed by applicants as SEQ ID NO: 2.

Feng et al do not disclose expression vectors or recombinant host cells comprising instant SEQ ID NO: 2. Fraser et al disclose the cloning, sequencing, and expression of the wild-type human alpha-2A-AR gene (see entire reference, especially page 11755). Fraser et al disclose that expression of the gene required cloning of the gene into an expression vector (pSVL) and transfection of the clone into cells to allow for production of protein (see page 11755, left column). Fraser et al teach the use of such cells and proteins produced in this manner in binding assays and activity assays to determining the affinity for and affect of agonists and antagonists on the alpha-2A-AR (see, e.g., pages 11757-11759). In view of the teachings of Fraser et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have cloned the isolated polynucleotide of Feng et al into an expression vector

and to have transfected that clone into a cell, thereby producing both an expression vector and a recombinant host cell comprising instant SEQ ID NO: 2. An ordinary artisan would have been motivated to have made such a modification in order to have obtained expression vectors and cells for use in assaying the affinity of the variant alpha 2A-AR protein for various agonists and antagonists and assaying the effects of such agents on the activity of the variant protein, as disclosed by Fraser et al, for the advantage of determining the functional properties of the variant protein disclosed by Feng et al, and for the further advantage of identifying any differences in affinities or activity in the variant protein as compared to the known wild-type alpha-2A-AR receptor. With further respect to claims 63 and 65, it is noted that it is a property of instant SEQ ID NO: 2 that it encodes the amino acid sequence of instant SEQ ID NO: 4. Accordingly, it would be a property of the recombinant host cells and expression vectors suggested by Feng et al and Fraser et al that they would express instant SEQ ID NO: 4.

Conclusion

18. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

In a reference published subsequent to the filing of the instant application, Small et al (The Journal of Biological Chemistry 275(49):38518-38523 [12/2000]) disclose the Lys251 variant of the alpha-2A adrenergic receptor described in the application (see entire reference). Small et al also disclose that the sequence deposited as GenBank Accession No. AF281308 is the alpha-2A adrenergic receptor gene sequence including the "sequence corrections illuminated by Guyer," referring to the Guyer et al reference

discussed above (see page 38519, left column of Small et al). An alignment of Accession No. AF281308 with instant SEQ ID NOs: 1 and 2 illustrates the fact that Accession No. AF281308 includes a sequence that is 100% identical to instant SEQ ID NO: 1, and identical to SEQ ID NO: 2 with the exception of having a C rather than a G at the position corresponding to position 753 of instant SEQ ID NO: 2 (see the alignments enclosed herewith).

Sequence search results are cited to show the sequence identity shared between the sequence taught by Fraser et al (deposited as GenBank accession no. M23533) and instant SEQ ID Nos 1 and 2, and the sequence identity shared between the sequence taught by Small et al (deposited as GenBank accession no. AF281308) and instant SEQ ID Nos 1 and 2.

It is also noted that both the specification (at, e.g., page 2), and the prior art as exemplified by Kobilka et al (Science 238(4827):650-656 [10/1987]; see entire reference, particularly page 655) disclose that the human alpha-2A adrenergic receptor gene is located on chromosome 10.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers

for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
April 4, 2003